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Management of acute and chronic HCV infection in persons with HIV coinfection

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Summary

Due to shared routes of transmission, acute and chronic infection with hepatitis C virus is common among persons living with HIV infection in many regions of the world. In the era of effective antiretroviral therapy, acute HCV infection has been increasingly recognized in HIV-infected persons, particularly men who have sex with men, and liver disease, including hepatocellular carcinoma, has emerged as a leading cause of morbidity and mortality in those with chronic HCV infection, particularly older adults with long-standing coinfection. Over the past decade, the foundation for the management of acute and chronic HCV infection has been interferon alfa. However, due the high burden of treatment-related side effects and low likelihood of sustained virologic response, the impact of treatment with peginterferon/ribavirin on the burden of HCV disease in has been limited. However, the anticipated availability of safe, tolerable and highly efficacious interferon-free, oral HCV direct-acting antiviral combination therapies promise to dramatically change the management of acute and chronic HCV infection in HIV-infected persons. Preliminary data from studies of such oral DAA regimens in HIV/HCV coinfected patients suggest that coinfection with HIV will not impair HCV cure with these regimens. Indeed, in the coming era of high effective oral HCV DAA treatments, the only special feature concerning treatment of acute and chronic HCV infection in HIV-infected patients may be drug interactions between the antiretroviral drugs for HIV infection and direct-acting antiviral drugs for HCV infection.

Keywords: HIV; HCV; Interferon; Direct-acting antivirals; Protease inhibitors; Polymerase inhibitors; NS5A inhibitors.
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Abbreviations: HCV, hepatitis C virus; DAAs, direct-acting antivirals; MSM, men who have sex with men; SVR, sustained virologic response.

Introduction

Due to shared routes of transmission, acute and chronic coinfection with hepatitis C virus (HCV) is common among persons living with HIV infection in many regions [1,2]. In the setting of effective antiretroviral therapy, acute HCV infections have been increasingly recognized among HIV-infected men who have sex with men, leading to revised recommendations for HCV screening and prevention among persons at risk for hepatitis C [3–7]. Further, since the treatment of chronic HCV infection has historically been substantially more difficult than that of acute HCV infection, strategies for the management of acutely infected patients with HIV coinfection have been guided by the goal of preventing the transition of acute to chronic infection [8–10]. However, ~25% of HIV-infected persons with acute hepatitis C will spontaneously resolve their HCV infection during the initial months following exposure, and emerging treatments for chronic HCV infection with oral direct-acting antivirals (DAAs) promise to erase the historical differential in HCV cure, following treatment in the acute and chronic phase of infection [11,12]. With the removal of interferon, the management of acute HCV infection in HIV-infected persons is expected to change dramatically in the era of HCV DAAs [13].

Similarly, the management of HIV-infected patients with chronic HCV infection can also be expected to change with the advent of new therapies. In the era of effective antiretroviral therapy, liver disease due to chronic HCV infection is a leading cause of morbidity and mortality, particularly among older adults with long-standing coinfection [14,15]. There is emerging evidence that successful antiviral treatment of HIV infection and HCV infection may reduce the risk of liver disease progression to cirrhosis and of its complications [1,16]. Suppression of HIV replication, leading to immune restoration and reduction in systematic inflammation, may slow liver disease progression [17–22]. As such, expert guidelines recommend antiretroviral therapy for most HIV/HCV coinfected persons, regardless of CD4 cell count [9,23,24]. Similarly, HCV treatment leading to HCV cure is strongly associated with a reduced risk of serious liver disease, including end-stage liver disease, hepatocellular carcinoma and liver-related death [10,11]. For more than a decade, HCV treatment with peginterferon/ribavirin has been recommended for coinfected patients at risk for significant hepatitis-related fibrosis [25–27]. However, on a population level, the effectiveness and overall impact of interferon-based HCV therapy has been negligible due to low treatment uptake in many settings [28,29].

This lack of effectiveness has been the result of the significant side effects associated with interferon and low HCV cure rates, compared to persons without HIV coinfection [25,27,30–32]. The advent of oral HCV direct-acting antivirals has been accompanied by a sense of optimism regarding the treatment of HIV/HCV coinfected HCV persons. Because these agents directly target HCV non-structural proteins (NS3/4A protease, NS5B polymerase, and NS5A protein) that have critical roles in the HCV life cycle, oral combinations of such agents have minimized the negative impact of host factors, such as race/ethnicity, *IL28B* genotype and HIV coinfection on the likelihood of HCV cure. Indeed, preliminary data from clinical trials of HCV direct-acting antivirals in combination with ribavirin or peginterferon/ribavirin or other oral HCV DAAs have demonstrated similar HCV cure rates in HIV-infected and HIV-uninfected persons, supporting the hypothesis that coinfection with HIV will not impair HCV cure with these regimens (Table 1) [33–39].

The purpose of this review is to address clinically relevant topics related to the management of acute and chronic HCV infection in HIV-infected patients in the era of highly effective, oral HCV direct-acting antiviral therapy.

Key Points

- Due to shared modes of transmission, acute and chronic infection with hepatitis C virus is common in persons with HIV infection
- In the era of effective antiretrovirals, the incidence of acute HCV infection has increased among HIV-infected men who have sex with men, leading to recommendations for enhanced screening and prevention
- Morbidity and mortality due to prevalent chronic HCV infection among HIV-infected persons has also increased, leading to recommendations for more aggressive treatment of both HIV and HCV infections
- HCV treatment with regimens containing direct-acting antivirals has been very promising in HIV-infected persons, with high HCV cure rates observed. These novel HCV treatments are expected to transform the management of both acute and chronic HCV infection in this population

Overview of HCV direct-acting antivirals

Multiple oral direct-acting antiviral agents are currently approved or being developed for the treatment of HCV infection [40]. In contrast to interferon alfa, which targets type 1 interferon receptors, found on many types of human cells, these drugs target the virus directly, leading to the expectation that co-infection with HIV will not impair their efficacy [41]. HCV DAAs can be classified according to their target in the HCV lifecycle: N3/4A protease, NS5A, NS5B polymerase, NS4A, NS4B, P7, and viral entry. While drug candidates have been identified for inhibition of P7 (e.g., BIT225), NS4A (e.g., ACH-1095), NS4B (e.g., clemizole), and viral entry (e.g., ITX-5061), the drug candidates/targets that have advanced into clinical practice or late stage trials include: inhibitors of NS3 protease, NS5A protein, and NS5B polymerase.

Inhibitors of NS3 protease

This class of agents has the distinction of being the first DAAs approved for use in HCV infected patients, providing validation of the *in vitro* models of anti-HCV activity. The initial approved agents, boceprevir and telaprevir, are administered thrice daily and have been characterized by potent antiviral activity against genotype 1 and 2 with less activity against genotype 3 [42–44]. In addition, studies of telaprevir monotherapy or with peginterferon alone (no ribavirin) witnessed the rapid emergence of variants with decreased susceptibility to the protease inhibitor, necessitating the co-administration of other HCV drugs, initially peginterferon/ribavirin [45]. Following these initial agents, simeprevir was approved in combination with peginterferon/ribavirin, providing important advantages over the first protease inhibitors. Simeprevir is a potent inhibitor of the NS3 protease, administered once daily and, unlike telaprevir and boceprevir, does not cause anaemia [46,47]. Additional potent NS3 protease inhibitors, administered once or twice daily (with or without ritonavir boosting), are in late stage development, including: ABT450/ritonavir, asunaprevir and MK-5172 [48,49]. These next generation drugs are being developed as part of interferon sparing combination regimens with other oral HCV DAAs that target other HCV non-structural proteins.

Inhibitors of NS5A protein

Since NS5A does not have enzymatic activity, the mechanism of action of this class is incompletely understood; however, studies indicate that these DAAs inhibit HCV replication as well as the assembly and release of infectious virions [50]. Multiple NS5A inhibitors are in late stage clinical development, including daclatasvir, ledipasvir, ombitasvir, and MK-8742. The first agent reported in this class, daclatasvir, demonstrated rapid and profound HCV RNA suppression after a single dose administered as monotherapy [51]. Importantly, Lok and co-workers evaluated the interferon-free combination of daclatasvir plus asunaprevir (NS3 protease inhibitor) in patients with HCV genotype 1 who had failed prior peginterferon/ribavirin therapy, providing the first evidence that chronic HCV infection could be eradicated without interferon [52]. Subsequently, NS5A inhibitors have emerged as critical components of several oral HCV DAA regimens which have completed phase 3 clinical development and are expected to be approved for clinical use [53–60].

Nucleosidic inhibitors of NS5B polymerase

This class of DAAs are nucleos(t)ide analogues that target the highly conserved active site of the HCV polymerase and are incorporated by the polymerase into the HCV RNA intermediate, leading the chain termination. *In vitro* and *in vivo*, these agents have been characterized by anti-viral activity against multiple HCV genotypes and a high barrier to the selection of resistant variants [61]. The first agent in this class, approved for clinical use, was sofosbuvir; this DAA is administered once daily, has few side effects and has been highly effective in combination with ribavirin or peginterferon/ribavirin or NS5A inhibitors (daclatasvir, ledipasvir) or NS3 protease inhibitors (simeprevir) [62–64]. The combination of sofosbuvir and ledipasvir has been coformulated as a single, oral fixed-dose combination tablet; in three phase 3 clinical trials (ION-1, ION-2, ION-3). 8 or 12 weeks of this

Table 1. Completed or ongoing clinical trials for HCV direct-acting antiviral regimens for a previously untreated HCV genotype 1 infection in HIV-infected adults.

Direct-acting antiviral agent (Oral)	PegIFN (injection)	Ribavirin (oral)	Treatment	Sustained virologic response (%)
Telaprevir 750 mg every 8 h [34]	Alfa-2a 180 μg/wk	1000 or 1200 mg/d	48 wk (telaprevir for the initial 12 wk only)	74
Boceprevir 800 mg every 8 h [33]	Alfa-2b 1.5 μg/kg per wk	600-1400 mg/d	48 wk (48 wk for PegIFN and ribavirin; 44 wk for boceprevir)	63
Simeprevir 150 mg once daily [39]	Alfa-2a 180 μg/wk	1000 or 1200 mg/d	24 or 48 wk (simeprevir for the initial 12 wk only)	79
Sofosbuvir 400 mg once daily [38]	Alfa-2a 180 μg/wk	1000 or 1200 mg/d	12 wk (all drugs)	89
Sofosbuvir 400 mg once daily [35]	None	1000 or 1200 mg/d	24 wk (all drugs)	76
Fixed-dose combination of sofosbuvir/ledipasvir (400/90 mg) one tablet daily	None	None	12 wk	Pending NCT01878799
Sofosbuvir 400 mg/d plus daclatasvir 30 or 60 or 90 mg once daily	None	None	8 or 12 wk	Pending NCT02032888
Fixed-dose combination of ABT-450/ritonavir/ombitasvir (150/100/25 mg) once daily plus dasabuvir 250 mg twice daily	None	1000 or 1200 mg/d	12 or 24 wk	Pending NCT01939197
Fixed dose combination MK-5172/MK-8742 (100/50 mg) one tablet once daily	None	None	12 wk	Pending NCT02105662

PegIFN, peginterferon; d, days; wk, weeks, h, hours.

combination led to HCV cure in more than 94% of HIV-uninfected patients with HCV genotype 1 infection [53–55].

Non-nucleosidic inhibitors of NS5B polymerase

In contrast to nucleos(t)ide inhibitors, non-nucleoside inhibitors bind to one of 4 allosteric sites (Thumb II and II; Palm I and II) within NS5B, leading to inhibition of the enzyme [65]. This DAA class has been characterized by moderate antiviral activity, which is genotype/subtype specific and has been associated with the rapid selection of resistant variants with monotherapy. These DAAs have emerged as important components of several interferon-free, oral HCV regimens, including dasabuvir that has been developed in combination with ABT450/ritonavir/ombitasvir, and beclabuvir (BMS-791325) that has been developed in combination with asunaprevir/daclatasvir [58,66–68].

Acute hepatitis C virus infection

Epidemiology

The most efficient route of HCV transmission is parenteral via contaminated blood or blood products. Among persons who inject drugs, coinfection may have been acquired via drug injection by syringe or other injection paraphernalia (i.e., "cookers," filters, or water) previously used by an infected person [69]. Although less efficient, HCV also can be transmitted sexually, especially between HIV-infected men who have sex with men (MSM). Over the past decade, acute HCV infections have increasingly been recognized among MSM in urban regions of Europe, Australia and the United States [3]. For example, in a study of twelve European HIV cohorts that included more than three thousand HIV-infected MSMs, the incidence of HCV seroconversion increased from 1990 (0.9–2.2 cases/1000 person years) to 2007 (23.4–51.1 cases/1000 person-years) with the greatest rise occurring after the advent of antiretroviral therapy [5]. Sexual acquisition of HCV infection has been associated with high-risk sexual behaviour (including unprotected anal intercourse and fisting) and non-injection drug use. In addition, the practice of serosorting or identifying sex partners according to HIV status has been linked to higher rates of high-risk behaviour among HIV-infected seroconcordant partners, leading to transmission of other sexually transmitted infections including HCV [2,6,70–72]. In addition, sexual transmission of HCV may also be facilitated by the effect of HIV on hepatitis C viraemia (higher viral load) and the presence of mucosal alterations by other sexually transmitted pathogens (e.g., herpes simplex or syphilis).

The increased recognition of acute HCV infection has prompted revisions to recommendations for screening, including annual HCV antibody testing in HIV-infected persons who are seronegative for HCV and monitoring of serum alanine aminotransferase (ALT) levels every three to six months [9,73]. In addition, HCV-seronegative patients must be counselled regarding the risk of sexual HCV acquisition and, although the effectiveness of male condoms in reducing HCV transmission is not known, barrier precautions are strongly recommended to reduce the risk of sexually transmitted diseases, including HCV.

Management of acute HCV infection

In 2011, the European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel published recommendations regarding the detection and management of patients with acute HCV infection [8]. The most strongly endorsed definitions of acute HCV infection were a positive HCV antibody (seroconversion) or a negative HCV antibody with detectable HCV RNA with documentation of a negative HCV antibody in the previous 12 months. Alternative definitions for persons for whom historical HCV antibody testing is not available include detectable HCV RNA and an acute rise is serum ALT levels coupled with exclusion of other causes of hepatitis.

Following the identification of acute HCV infection, strategies for management have been based on the likelihood of spontaneous HCV clearance. In general, HIV coinfection has been associated with lower HCV clearance following acute infection. In one, largely African-American cohort in Baltimore, Maryland, HCV clearance was observed in 7% and 14% of patients with and without HIV coinfection, respectively [74]. On the other hand, in the EuroSIDA cohort, HCV RNA was not detected in 23% of nearly two thousand HCV seropositive, HIV-infected patients [75]. More recently, these variable rates of HCV clearance have been explained, in part, by the identification of single a nucleotide polymorphism (SNP) on chromosome 19 upstream of the gene for *IL28B* (rs12979860) that is strongly associated with spontaneous HCV clearance [11]. Interestingly, in the first study that demonstrated a relationship of the *IL28B* genotype and spontaneous HCV clearance, Thomas and colleagues did not observe a difference in the rate of HCV clearance in HIV-infected and HIV-uninfected persons after accounting for the *IL28B* genotype [11]. Among patients with the *IL28B* CC genotype, the frequency of HCV clearance was similar in both HIV-infected (52.2%) and HIV-uninfected patients (53.1%). However, the temporal sequence of the acquisition of each infection may be an important factor that is incompletely accounted for in studies that rely on cross-sectional data. In many settings and in prior studies, HCV infection was acquired and cleared or not cleared prior to infection with HIV. Importantly, with the current epidemic of acute HCV infection in HIV-infected persons, the temporal sequence of infection is reversed (HIV first, HCV second), which has been associated with lower rates of spontaneous HCV clearance [76]. Thus, in the era of effective antivirals and the understanding of host determinants, the impact of HIV infection on the likelihood of spontaneous HCV clearance is uncertain since earlier studies did not account for the *IL28B* genotype and later studies are confounded by the HCV treatment during the acute phase of infection.

However, following the identification of the importance of the *IL28B* polymorphism, several groups of investigators have developed clinical tools to predict the likelihood of spontaneous clearance for individual patients. At the time of acute HCV diagnosis, the presence of *IL28B* CC genotype, female sex and the presence of jaundice are strongly associated with subsequent HCV clearance [77,78]. In addition, significant decline in serum HCV RNA levels over the initial four weeks following HCV diagnosis has been associated with higher likelihood of spontaneous clearance [79]. Based on these observations, the NEAT panel recommended that patients in whom the HCV RNA did not decline by at least 2 $\log_{10}$ or in whom HCV RNA was detected more than 12 weeks after the diagnosis should be offered HCV treatment. On the other hand, because of the high likelihood of HCV clearance with treatment during the acute phase, a United States panel recommended that HIV-infected patients with acute HCV infection should be offered HCV treatment [9].

Both the European and United States panels recommend treatment with peginterferon/ribavirin for 24 or 48 weeks with shorter durations of therapy for patients who achieve rapid virologic response (HCV RNA not detected after four weeks of treatment. This recommendation was based on data, derived from multiple, uncontrolled trials of peginterferon/ribavirin therapy, HCV eradication was achieved in more than 75% of HIV-infected patients with acute HCV infection, which was substantially higher than the HCV cure rates achieved in HIV-infected patients with chronic HCV infection, treated with the same regimen ~ approximately 40% or less [10,80–82]. Thus, in the era of peginterferon/ribavirin, the decision to initiate treatment for acute HCV infection in HIV-infected persons represented the careful consideration of the likelihood of spontaneous clearance and the need to intervene with HCV treatment prior to the loss of responsiveness to interferon alfa that is observed in the chronic phase of HCV infection.

Role of HCV direct-acting antivirals for acute HCV infection

While there are very limited data on the use of HCV DAAs for the treatment of acute HCV infection, Fierer and colleagues reported HCV cure in 16 of 19 (84%) HIV-infected men, treated for acute HCV genotype 1 infection with telaprevir (NS3 protease inhibitor) plus peginterferon/ribavirin. Additional studies of HCV DAAs for acute HCV infection are in development or underway. For example, the Dutch Acute HCV in HIV Study (DAHHS) is underway to assess the efficacy of 12 weeks for boceprevir (NS3 protease inhibitor) plus peginterferon/ribavirin for the treatment of acute HCV genotype 1 in HIV-infected patients (ClinicalTrials.gov Identifier: NCT01912495). In the United States, the SWIFT-C study is currently underway to examine the safety and efficacy of the nucleotide analogue HCV NS5B polymerase inhibitor, sofosbuvir plus ribavirin) for the treatment of HIV-infected persons with acute HCV infection (ClinicalTrials.gov Identifier: NCT02128217). In Australia, the DAA-based Therapy for Recently Acquired Hepatitis C II study (DARE C II) will also assess the combination of sofosbuvir plus ribavirin for the treatment of acute HCV infection (ClinicalTrials.gov Identifier: NCT02156570).

In contrast to the limited data in the acute setting, large, phase 3 clinical trials of oral HCV DAAs for chronic HCV infection have been completed, demonstrating excellent tolerability and safety, as well as HCV cure rates in excess of 95%, following 12 weeks of interferon-free therapy [53,60]. Further, traditional predictors of poor response to peginterferon/ribavirin (e.g. race/ethnicity, obesity, HCV RNA level, *IL28B* genotype, and HIV status) were not associated with lower response to these oral, HCV DAA regimens. Thus, as the treatment of chronic HCV infection shifts to incorporate these oral HCV regimens, the management of patients with acute HCV may also change since the primary reason to rapidly start HCV treatment has been to prevent the transition from the acute phase to the chronic phase of infection, which has been associated with poor interferon alfa response. Although the optimal approach to the management of acute HCV infection in HIV-infected persons will need to be determined through clinical trials, cost-effectiveness analysis and expert consensus, at least two strategies may be considered: (1) early

intervention with a short course (e.g., 4 weeks duration) of oral HCV DAAs; or (2) delayed intervention (e.g., up to 24 weeks following diagnosis) to allow for spontaneous HCV clearance, followed by treatment of persons with persistent HCV infection with oral HCV DAAs for the duration recommended for chronic HCV infection. Regardless of strategy, all patients who clear acute HCV infection with or without treatment must be educated regarding the risk of reinfection, and measures should be implemented to reduce the risk of reinfection [83]. In addition, these HCV seropositive, HCV RNA negative patients should be monitored with serum ALT and/or HCV RNA testing following spontaneous or treatment induced clearance [84].

Chronic hepatitis C virus infection

Peginterferon/ribavirin

Based on multiple randomized controlled clinical trials, peginterferon/ribavirin is approved in many regions for the treatment of chronic HCV infection [25–27,85]. Among patients who were eligible for interferon-based treatment, the safety and tolerability profile of peginterferon/ribavirin has been similar in persons with and without HIV coinfection. While drug interactions with antiretrovirals are uncommon, zidovudine is not recommended due to additive bone marrow suppression, leading to worsening of neutropenia and anaemia. Also, ribavirin increases exposure to the active metabolite of didanosine which has caused clinical toxicities, including pancreatitis, lactic acidosis, and peripheral neuropathy; as such, its use is contraindicated [86]. In addition to toxicity, the major limitation of peginterferon/ribavirin has been the low rates of HCV cure in HIV-infected patients compared to HIV-uninfected patients. For example, in the APRICOT and RIBAVIC studies in HIV-coinfected patients, the sustained virologic response (SVR) rates for genotype 1 were 29% and 20%, respectively [25,85]. By comparison, in the study by Hadziyannis and colleagues, HCV monoinfected patients treated with the same regimen as those in the APRICOT trial (fixed-dose ribavirin, 800 mg/day) had higher sustained virologic response rates than HIV coinfected patients (genotype 1, 41% >29% SVR) [87]. The poor response in coinfected patients was most evident in those with genotype 1 infection and high HCV RNA levels (>800,000 copies/ml) in whom the SVR rate was only 18% compared to 36% for similar patients without HIV coinfection. Since many HIV/HCV coinfected patients with HIV/HCV coinfection have relatively high HCV RNA levels and multiple relative or absolute contraindications to peginterferon/ribavirin, the effectiveness of this regimen has been low in this population, leading to the characterization of coinfected patients as "difficult to treat" [28,88].

Direct-acting-antivirals for chronic HCV infection

By targeting the virus rather than the host, direct-acting antivirals may improve both efficacy and tolerability in HIV-infected patients; indeed, in several clinical trials, DAAs have shown great promise in this population. Multiple studies have demonstrated high response rates with peginterferon/ribavirin plus a single DAA, including HCV protease inhibitors (e.g., telaprevir, boceprevir, simeprevir) and the nucleotide analogue polymerase inhibitor sofosbuvir [35,36]. Further, data from studies of interferon-free, oral DAA therapy have been reported with the observation of high SVR rates and excellent tolerability. Taken together, these emerging data support the hypothesis that HIV coinfection does not adversely impact the effectiveness of DAA therapy.

Boceprevir plus peginterferon/ribavirin

In treatment-naïve, HIV-uninfected patients with genotype 1 infection, following a 4 week lead-in phase of peginterferon/ribavirin, boceprevir 800 mg every 8 h plus peginterferon/ribavirin for 44 weeks achieved SVR in 68%; the SVR rate among placebo-treated patients was 40% [43]. In a double-blind, randomized phase 2 trial, the same regimen was evaluated in treatment-naïve, HIV-infected patients with HCV genotype 1 coinfection. In this trial, 98 HIV/HCV-coinfected patients were randomly assigned to receive the same regimen with a 4 week lead-in phase, followed by 44 weeks of boceprevir (n = 64) or placebo (n = 34) [33]. On the basis of the initial drug interaction studies in healthy volunteers, patients receiving efavirenz were excluded; patients with undetected HIV RNA, taking ritonavir-boosted HIV protease inhibitors (darunavir, atazanavir, and lopinavir) and the HIV integrase inhibitor, raltegravir, were enrolled. However, after the study commenced, additional drug interaction studies demonstrated potentially significant bidirectional interactions between HIV-1 protease inhibitors and boceprevir, leading to recommendations against their co-administration [89]. The majority of patients were male (65%–72%), white (81%–82%), and infected with genotype 1a, (74%–80%). The median CD4 cell count was relatively high (577–586 cells/mm^3). Similar to the findings in HIV-uninfected patients, the SVR rate was 62% in the boceprevir-treated patients and 29% in the placebo-treated patients. Although this study population was relatively small, no difference in HCV response or HIV breakthrough was detected among patients treated with ritonavir-boosted HIV protease inhibitors and other antiretrovirals, despite the expectation of lower drug concentrations, due the interaction between HIV protease inhibitors and boceprevir. Similar to patients without HIV coinfection, adverse events were more common among patients who received boceprevir compared to those who received placebo; patients taking boceprevir experienced more anaemia, neutropenia, fever, anorexia, and gastrointestinal symptoms. Discontinuation of HCV treatment due to adverse events was also more common in boceprevir-treated patients (20%) compared with placebo-treated patients (9%).

In a second study, ANRS-HC27 BocepreVIH, 64 HIV-infected patients with HCV genotype 1 who had failed to respond to prior peginterferon/ribavirin therapy were treated with boceprevir plus peginterferon/ribavirin. The total duration of HCV treatment was either 48 or 72 weeks based on the HCV RNA response at treatment week 8 [90]. Enrolled patients received either atazanavir/ritonavir (n = 32) or raltegravir (n = 27) with frequent HIV RNA monitoring for patients taking atazanavir. The SVR rate was 53% (34 of 64 patients), which was similar to the response observed in a similar population of HIV uninfected patients [91]. The safety and tolerability profile was similar to the prior studies; ten patients stopped therapy due to adverse events. No HIV RNA breakthrough was observed.

Telaprevir plus peginterferon/ribavirin

In treatment-naïve, HCV genotype 1 infected patients without HIV infection, telaprevir 750 mg every 8 h (12 weeks) for

12 weeks in combination with peginterferon/ribavirin for 24 or 48 weeks achieved a SVR rate of 75%; the SVR rate among placebo-treated patients was 45% [12]. In a double-blind, randomized phase 2 trial, the same regimen was evaluated in treatment-naïve, HIV-infected patients with genotype 1 coinfection [34]. Patients were randomized to 12 weeks of peginterferon/ribavirin plus telaprevir (n = 38) or placebo (n = 22), followed by 36 weeks of peginterferon/ribavirin; all patients were treated for 48 weeks (no response-guided therapy). On the basis of drug interaction studies in healthy volunteers, enrolled patients received either no antiretroviral therapy (n = 13) or atazanavir/ritonavir (n = 23) or efavirenz (n = 24); patients receiving efavirenz were treated with higher telaprevir doses (1125 mg every 8 h) to offset the reduction in telaprevir levels by efavirenz. The majority of patients were male (67%–100%), white (29%–87%), and infected with genotype 1a (43%–80%). The median CD4 cell count was high (514–675 cells/mm^3). Similar to the findings in HIV-uninfected patients, SVR was achieved in 74% of the telaprevir-treated patients compared with 45% in placebo-treated patients. Adverse events were more frequently observed with telaprevir. Specifically, telaprevir was associated with pruritus, dizziness, headache nausea, rash, and anaemia. However, discontinuation of HCV treatment study drugs because of adverse events was uncommon (telaprevir, 3 patients). Further, no adverse impact on HIV or its treatment with antiretroviral therapy was detected.

In a second study, ANRS HC26 TelapreVIH, 69 HIV-infected patients with genotype 1 coinfection who had failed prior peginterferon/ribavirin therapy were treated with a 4 week lead-in of peginterferon/ribavirin, followed by 12 weeks of telaprevir plus peginterferon/ribavirin [92]. The total duration of HCV treatment was either 48 or 72 weeks based on the HCV RNA response at treatment week 8. Patients received HIV treatment that included either atazanavir/ritonavir (n = 34), efavirenz (n = 13) or raltegravir (n = 17). The majority of patients (99%) had suppressed HIV RNA and the median CD4 cell count was 630 cells/mm^3. Similar to responses previously observed in HIV-uninfected patients, the SVR rate with this regimen was 80% [42,93]. Although 20% of patients stopped HCV treatment due adverse events, the safety and tolerability profile was consistent with prior studies.

Simeprevir plus peginterferon/ribavirin

Simeprevir plus peginterferon/ribavirin has been evaluated in HIV-infected and uninfected patients with HCV genotype 1 coinfection. In the QUEST-1 and QUEST-2 studies, treatment-naïve, HIV uninfected patients were randomized to simeprevir 150 mg daily or placebo for 12 weeks plus peginterferon/ribavirin for 24 or 48 weeks response-guided therapy; the SVR rate was 80% in simeprevir-treated patients and 50% in placebo-treated patients [46,47]. Study C212 evaluated the same simeprevir-based regimen in 106 HIV-infected patients with genotype 1 coinfection [39]. Treatment-naïve patients without cirrhosis (n = 50) and those who had relapsed after prior peginterferon/ribavirin therapy (n = 14) had response-guided therapy whereas patients who had partial or null response during prior peginterferon/ribavirin therapy (n = 38) and those with cirrhosis (n = 4) were treated for 48 weeks. Based on drug interaction studies in healthy volunteers, HIV protease inhibitors were not permitted; enrolled patients received rilpivirine, raltegravir, maraviroc, enfuvirtide or were not taking antiretroviral. The majority of patients were male (85%) and infected with HCV genotype 1a (82%). Similar to the findings in HIV-uninfected patients, the overall SVR rate was 74%; most treatment-naïve patients were treated for 24 weeks and had higher SVR rates (79%) than patients with prior null response, treated for 48 weeks (57%). The safety and tolerability profile was similar to that observed in HIV-uninfected patients; rash/photosensitivity was reported in 16 patients during the simeprevir phase of the study. Four patients discontinued HCV treatment due to adverse effects.

Sofosbuvir plus peginterferon/ribavirin

In the NEUTRINO study, treatment-naïve, HIV-uninfected patients with genotype 1, 4, 5 or 6 infection, who received sofosbuvir 400 mg daily plus peginterferon/ribavirin for 12 weeks achieved a SVR rate of 90% and, in patients with genotype 1 infection, the SVR rate was 89% [62]. Rodriguez-Torres and co-workers conducted a similar study of 12 weeks of treatment with sofosbuvir plus peginterferon/ribavirin in 23 HIV-infected patients with genotype 1 (n = 19), 2 (n = 1), 3 (n = 2), and 4 (n = 1) coinfection [38]. Based on the absence of drug interactions in healthy volunteers, patients received antiretroviral regimens containing darunavir/ritonavir, raltegravir, efavirenz or rilpivirine. The majority of patients were male (78%) and had high CD4 cell counts (mean 563 cells/mm^3). Similar to the findings in HIV-uninfected patients, the overall SVR rate was 91% and, in patients with genotype 1 infection, the SVR rate was 89%. Two patients stopped HCV treatment due to of adverse events (anaemia and altered mood); no serious adverse events were reported. Overall, the safety and tolerability profiles were similar to that observed in the study of HIV-uninfected patients.

Sofosbuvir plus ribavirin

In the SPARE study, sixty HIV-uninfected patients with HCV genotype 1 infection were treated with sofosbuvir 400 mg daily plus weight-based or low dose ribavirin for 24 weeks. Among patients treated with weight-based ribavirin, Osinusi and co-workers reported that 68% achieved SVR whereas lower SVR rates were observed with low dose ribavirin [42]. Similarly, in the FISSION study, HIV-uninfected persons with HCV genotype 2 and 3 infection were treated with sofosbuvir plus ribavirin for 12 weeks leading to SVR in 97% of patients with genotype 2 infection and in 56% of those with genotype 3 infection [21]. In the VALENCE study, HIV-uninfected persons with HCV genotype 3 infection were treated with sofosbuvir plus weight-based ribavirin for 24 weeks, leading to SVR in 85% of treatment-naïve and treatment experienced patients [94].

In the PHOTON-1 study, the same regimen sofosbuvir and weight-based ribavirin was evaluated in 223 HIV-infected patients with genotype 1, 2 or 3 infections [35]. The treatment duration was 24 weeks for treatment-naïve patients with genotype 1 (n = 114) and for, treatment-experienced patients with HCV genotype 2 (n = 24) or 3 (n = 17). Sixty-eight treatment-naive patients with HCV genotype 2 (n = 26) or 3 (n = 41) were treated for 12 weeks. Based on the lack of relevant drug interactions in healthy volunteer studies, patients received antiretroviral therapy containing efavirenz, atazanavir/ritonavir, darunavir/ritonavir, raltegravir and rilpivirine. The majority of patients enrolled were male (81%–91%) and taking antiretroviral therapy (90%–98%); the median CD4 cell count was high (585–658 cells/mm^3) and few

patients had cirrhosis (4%–24%). Among treatment-naïve patients, the SVR rates varied by genotype and were similar to the SVR observed in HIV-uninfected patients: genotype 1, 76%; genotype 2; 92%; genotype 3, 67%. Among treatment-experienced patients, the SVR rate was 92% for patients with genotype 2 and 88% for patients with genotype 3. The majority of virologic failures were patients with on-treatment response followed by viral relapse after stopping treatment; resistance to sofosbuvir was not reported in patients with virologic failure. Treatment discontinuation due to adverse effects was observed in 3% of patients treated for 24 weeks; the most commonly reported adverse events were fatigue, insomnia and headache. No adverse impact on HIV disease or its treatment with antiretroviral therapy was detected. However, hyperbilirubinemia was seen in two-thirds of patients taking atazanavir/ritonavir due to ribavirin-induced haemolysis, coupled with atazanavir-induced inhibition of human UDP-glucuronosyltransferase 1A (UGT1A). While this was not associated with clinical harm, four patients switched from atazanavir to darunavir. Anaemia (haemoglobin <10 grams/dl) occurred in 17% of patients treated for 24 weeks; no patients took epoetin alfa or had blood transfusions. Taken together, the findings of the clinical trials of sofosbuvir/ribavirin found similar rates of sustained virologic response in HCV genotype 1, 2, and 3 infected persons with and with HIV coinfection (Fig. 1).

Sofosbuvir plus ledipasvir

The fixed-dose combination of sofosbuvir/ledipasvir (one tablet daily) has been studied with and without ribavirin in HIV-uninfected persons with genotype 1 infection. In the ION-1 and ION-3 studies, treatment-naïve, HIV-uninfected patients were treated with sofosbuvir/ledipasvir with or without ribavirin for 8, 12 or 24 weeks [53,55]. Among patients treated with sofosbuvir/ledipasvir (no ribavirin), the SVR rates were: 8 weeks, 94% (ION-3); 12 weeks, 97% (ION-1 and ION-3); 24 weeks, 98% (ION-1). Among patients treated with sofosbuvir/ledipasvir plus ribavirin, the SVR rates were: 8 weeks, 93% (ION-3); 12 weeks, 97% (ION-1); 24 weeks, 98% (ION-1). In the ION-2 study, which enrolled HIV-uninfected patients with genotype 1 infection who had failed prior peginterferon/ribavirin with or without telaprevir or boceprevir, similar high SVR rates of 94% to 99% were observed with 12 or 24 weeks of sofosbuvir/ledipasvir with or without ribavirin [54].

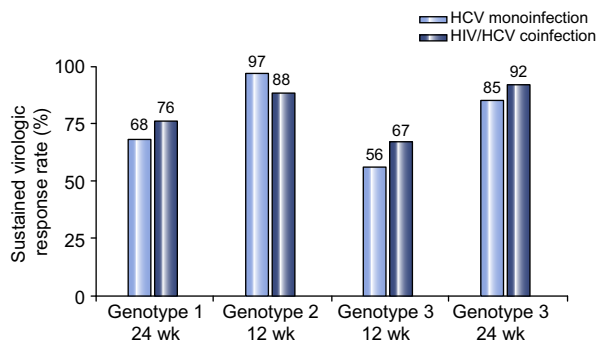

Fig. 1. Sustained virologic response rates observed with sofosbuvir/ribavirin therapy in HIV-infected and uninfected persons with HCV genotype 1 or 2 or 3 infection (data derived from three separate studies: Fission, Valence and Photon-1) [62,94,105].

Based on these studies in HIV-uninfected patients, 12 weeks of treatment with the fixed-dose combination of sofosbuvir/ledipasvir (no ribavirin) is under investigation in HIV-infected patients with genotype 1 or 4 infection. The ION-4 study, a phase 3, multicentre trial to evaluate 12 weeks of treatment with the fixed-dose combination of sofosbuvir/ledipasvir one tablet daily in HIV-infected persons coinfected with genotype 1 or 4, is underway (ClinicalTrials.gov Identifier: NCT02073656). In addition, sofosbuvir/ledipasvir will be evaluated for 24 weeks by the French National Institute for Health and Medical Research and the French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS) in HIV-infected patients who failed prior telaprevir or boceprevir plus peginterferon/ribavirin therapy (ClinicalTrials.gov Identifier: NCT02125500).

While these studies are underway, preliminary data on the safety, tolerability and efficacy of the fixed-dose combination of sofosbuvir/ledipasvir have been presented by researchers at the US National Institute of Health (NIH). In the ERADICATE study, Osinusi and colleagues evaluated 12 weeks of sofosbuvir/ledipasvir in 50 treatment-naïve, HIV-infected patients with genotype 1 coinfection [36]. Enrolled patients were either not being treated for HIV infection (CD4 >500 cells/mm^3) or had suppressed HIV RNA on antiretroviral therapy, containing tenofovir/emtricitabine plus efavirenz, raltegravir, or rilpivirine. The majority of patients was African-American (54%–81%) and infected with genotype 1a (75%–81%). The median CD4 cell count was high in patients with (n = 37; 576 cells/mm^3) or without (n = 13; 687 cell/mm^3) antiretroviral therapy. While final efficacy data have not been reported, HCV RNA suppression during treatment with sofosbuvir/ledipasvir was observed in all patients (100%) and, among the 34 patients who have been monitored for at least 4 weeks after stopping treatment, viral relapse has not been observed. The safety and tolerability profile of sofosbuvir/ledipasvir for 12 weeks was similar to that observed in HIV-uninfected patients; no patient discontinued treatment due to an adverse event; no serious adverse events were reported. While additional drug interaction studies are ongoing, three studies in healthy volunteers have assessed the interaction between the combination of sofosbuvir/ledipasvir and the combination of antiretroviral regimens including tenofovir/emtricitabine plus raltegravir, efavirenz or rilpivirine. Sofosbuvir/ledipasvir did not affect levels of efavirenz, rilpivirine, or emtricitabine; however, tenofovir exposure increased ~1.8 to 2.6-fold with efavirenz and ~1.3 to 1.9-fold with rilpivirine [95]. Because this magnitude of increase in tenofovir concentration is similar to that observed with HIV protease inhibitors, no dose adjustment of either treatment was recommended.

Sofosbuvir plus daclatasvir

In 211 HIV-uninfected patients with genotype 1, 2 or 3 infection, sofosbuvir plus daclatasvir 60 mg daily with or without ribavirin for 12 or 24 weeks led to a SVR in 98% of treatment-naïve (n = 126) and treatment-experienced (n = 41) patients with genotype 1, 92% of patients with genotype 2 (n = 26), and 89% of patients with genotype 3 (n = 18) [12]. In HIV-infected patients, the ALLY-2 study is underway to evaluate sofosbuvir plus daclatasvir for 8 or 12 weeks in HIV-infected patients with genotype 1, 2, 3, 4, 5 or 6 coinfection (ClinicalTrials.gov Identifier: NCT02032888). Drug interaction studies in healthy volunteers have been completed for daclatasvir and atazanavir/ritonavir, efavirenz and tenofovir. No relevant interactions between

Table 2. Antiretroviral drug interactions for HCV treatment that include approved or available direct-acting antivirals.

Drug	Notable antiretroviral drug-drug interactions	Acceptable antiretroviral
Non-specific agents		
PegIFNα [105, 106]	• None	All with the exception of: • Zidovudine due to additive bone marrow suppression and clinical worsening of pancytopenia
Ribavirin [107, 108]	• Didanosine	All with the exception of: • Zidovudine due to additive bone marrow suppression and worsening of anemia • Didanosine due to increased exposure the active metabolite of didanosine leading to lactic acidosis, hepatomegaly/steatosis, and pancreatitis *Note: Increased indirect hyperbilirubinemia may occur due to interaction of ribavirin induced hemolysis and atazanavir-induced inhibition of UGTA1A*
NS5B polymerase inhibitors		
Sofosbuvir [109]	• Tipranavir	All with the exception of: • Tipranavir due to the potential for decreased sofosbuvir exposure as a result of intestinal PgP induction
NS3 protease inhibitors		
Boceprevir [110]	• Darunavir/ritonavir and other HIV-1 protease inhibitors with or without ritonavir • Efavirenz • Cobicistat anticipated to have interactions similar to ritonavir (elvitegravir/cobicistat)	Data support the use of boceprevir in combination with: • Raltegravir or dolutegravir • Rilpivirine • Maraviroc - reduce dose to 150 mg twice daily • Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) including tenofovir, abacavir, emtricitabine, and lamivudine • Limited data support co-administration with atazanavir/ritonavir or with etravirine
Simeprevir [111]	• Darunavir/ritonavir and other HIV-1 protease inhibitors with or without ritonavir • Efavirenz • Cobicistat anticipated to have interactions similar to ritonavir (elvitegravir/cobicistat)	Data support the use of simeprevir in combination with: • Raltegravir (no data available for dolutegravir) • Maraviroc • Rilpivirine • Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) including tenofovir, abacavir, emtricitabine, and lamivudine
Telaprevir [98, 112]	• Darunavir or lopinavir or fosamprenavir with or without ritonavir	Data support the use of telaprevir in combination with: • Atazanavir/ritonavir • Raltegravir or dolutegravir or elvitegravir/cobicistat/tenofovir/emtricitabine • Rilpivirine or etravirine or efavirenz (increase telaprevir dose to 1125 mg every 8 hours with efavirenz • Maraviroc – reduce dose to 150 mg twice daily • Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) including tenofovir, abacavir, emtricitabine, and lamivudine
NS5A inhibitors		
Daclatasvir [96]	• None reported to date but published data has been limited.	Data support the use of daclatasvir in combination with: • Atazanavir/ritonavir with daclatasvir dose reduction to 30 mg once daily • Efavirenz with daclatasvir dose increase to 90 mg once daily • Tenofovir – no clinically relevant interactions observed

PegIFN, peginterferon.

daclatasvir and tenofovir were reported whereas daclatasvir exposures were higher with atazanavir/ritonavir and lower with efavirenz co-administration. Based on modelling, the researchers recommended daclatasvir dose adjustment to 30 mg daily with atazanavir/ritonavir and 90 mg once daily with efavirenz; this strategy was incorporated in the ongoing trials [96].

ABT450/ritonavir/ombitasvir plus dasabuvir

In HIV-uninfected patients with genotype 1 infection, the combination of ABT-450/ritonavir (protease inhibitor)/ombitasvir (NS5A inhibitor) plus dasabuvir (non-nucleoside polymerase inhibitor) has been evaluated with and without ribavirin in multiple phase 3 studies. Among patients without cirrhosis, 12 weeks of treatment with the three drugs plus ribavirin led to SVR in 96% of previously untreated patients (SAPPHIRE-I) and 96% of prior peginterferon/ribavirin treated patients (SAPHIRE-II) [57,58]. In the TURQUISE-II study, HIV-uninfected patients with genotype 1 infection and compensated cirrhosis were treated for 12 or 24 weeks with the three drugs plus ribavirin cirrhotic; SVR was achieved in 92% of cirrhotic patients treated for 12 weeks and in 96% of those treated for 24 weeks [59]. The role of ribavirin

in this regimen was assessed in the PEARL III and IV studies [60]. HIV-uninfected patients with genotype 1a and 1b were treated for 12 weeks with the three drugs plus placebo or ribavirin. In the PEARL-III study, treatment-naïve patients with HCV genotype 1b infection had a SVR rate of 99% with and without ribavirin. However, in the PEARL-IV study, treatment-naïve patients with HCV genotype 1a infection had a SVR rate of 97% with ribavirin and 90% without ribavirin; this difference was largely due to more virologic failure without ribavirin (7.8% compared to 2%).

Among HIV-infected patients with genotype 1 coinfection, the TURQUOISE-I study is underway to evaluate the safety and efficacy of the combination of ABT-450/ritonavir/ombitasvir plus dasabuvir plus ribavirin for 12 or 24 weeks duration (ClinicalTrials.gov Identifier: NCT01939197); data from this clinical trial is not yet available at this time. Drug interaction studies with the combination of ABT-450/ritonavir/ombitasvir plus dasabuvir and other drugs, including antiretrovirals, are underway.

MK-5172 plus MK8742

In HIV-infected and uninfected patients with genotype 1 infection, the once daily oral, two drug combination of MK-5172 (protease) plus MK-8742 (NS5A inhibitor) has been evaluated in a phase 2b study, C-WORTHY (ClinicalTrials.gov Identifier: NCT01717326). Interestingly, patients with and without HIV were enrolled under the same study protocol, underscoring the concept that these populations respond similarly to HCV treatment with DAAs. Recently reported results from the C-WORTHY study appear to support this hypothesis [37,97]. In one part of the study, treatment-naïve, non-cirrhotic, HIV-uninfected patients with genotype 1 infection were treated with 12 weeks of the combination of MK-5172 plus MK-8472 with or without ribavirin; the SVR rate was 94% in patients treated without ribavirin and 98% in those treated with ribavirin. In a second part of the study, treatment-naïve, non-cirrhotic, HIV infected patients (n = 59) were treated with same regimen. The majority were male (80%) and had infection with HCV genotype 1a (75%). Due to drug interactions with other antiretroviral regimens, patients were required to take raltegravir plus tenofovir or abacavir plus emtricitabine or lamivudine. Preliminary HCV response data have been reported. In the ribavirin-free arm (n = 30), one patient was lost to follow-up and two had HCV breakthrough; the SVR rate 4 weeks after stopping therapy was 90%. In the ribavirin-containing arm (n = 29), no HCV breakthrough was observed during treatment and one patient had a viral relapse after stopping therapy; the SVR rate 4 weeks after stopping the therapy was 97%. No adverse effect was detected on HIV disease or its treatment with antiretrovirals. Drug interaction studies with the combination of MK-5172 plus MK-8742 and antiretroviral drugs are ongoing. In addition, the phase 3, C-EDGE coinfection trial is underway and will evaluate the fixed-dose combination of MK-5172/MK-8742 (no ribavirin) for 12 weeks in HIV-infected patients with genotype 1, 4, 5, or 6 infection; patients are not permitted to receive the ritonavir boosted or unboosted HIV protease inhibitor, efavirenz or etravirine (ClinicalTrials.gov Identifier: NCT02105662).

Challenges to the use of direct-acting antivirals in HIV-infected patients

Although still preliminary, the available data indicate that the safety, tolerability and efficacy of interferon-containing and interferon-sparing DAA regimens will be similar in HIV-infected and uninfected patients. If this is confirmed in larger studies, only unique aspects for the management of HCV infection in persons with HIV coinfection may be needed to carefully consider the potential for drug interactions between the patient's antiretroviral drugs and the HCV direct-acting antiviral drugs (Table 2) [98–100]. For some patients' drug regimens, this may represent the combination of many unique antiviral drugs each with a different mechanism of action to inhibit HIV or HCV or to block antiviral drug metabolism through inhibition of the patient's cytochrome P450 pathways (e.g., ritonavir or cobicistat) [101,102]. As such, full understanding of possible drug interactions between HIV and HCV drug regimens will be required before these regimens can be safely combined. The expectation is due to irreconcilable drug interactions with some antiviral combinations. Not all antiretroviral regimens will be able to be safely combined with all HCV direct-acting antiviral regimens; as such, clinicians who treat patients with HIV/HCV coinfection will need to carefully select the most appropriate HIV and HCV treatment regimens for each patient on an individual basis. However, this challenge is mitigated by the finite and brief (12 weeks) nature of HCV treatment, leading to cure in most patients [103,104]. Thus, despite the potential for drug interactions between HCV direct acting antivirals and antiretroviral, most HIV/HCV coinfected patients will be able to benefit from these emerging therapies.

Conclusion

Due to shared routes of transmission, acute and chronic coinfection with HCV is common among persons living with HIV infection in many regions [1,2]. In the era of effective antiretroviral therapy, persons with acute HCV infection, particularly men who have sex with men, are increasingly detected and persons with chronic HCV infection, particularly older adults, are increasingly developing life-threatening complications of HCV disease including hepatocellular carcinoma and end-stage liver disease. Over the past decade, the foundation of strategies for the management of HIV-infected patient with acute or chronic HCV infection has been treatment with peginterferon alfa. The effectiveness of HCV treatment with peginterferon/ribavirin has been substantially limited by the high burden of treatment-related side effects and relatively low likelihood of HCV cure for many coinfected patients. The emergence of multiple direct-acting antiviral drugs and the regulatory approval of safe, tolerable and highly effective interferon-free HCV treatments will dramatically change the approach to HCV infection in HIV-infected persons. Preliminary data from studies of interferon-free, oral combinations of DAAs in HIV/HCV coinfected patients have been promising, supporting the hypothesis that coinfection with HIV will not impair HCV cure with these regimens. In the coming era of high effective HCV treatment, the only special feature of management of coinfected patients may be drug interactions between antiretrovirals and DAAs. As such, a complete understanding of the pharmacokinetics of antiviral drug regimens will be essential for the treatment of HCV in patients with HIV coinfection.

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Conflict of interest

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